(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 699 436 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
13.06.2001 Bulletin 2001/24

(51) Int Cl.[7]: **A61K 31/135**, A61K 9/16, A61K 9/20

(21) Application number: **95114527.5**

(22) Date of filing: **29.04.1994**

(54) **Controlled release formulation**

Arzneimittel mit kontrollierter Wirkstoffabgabe

Composition à libération contrôlée

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE

(30) Priority: **10.05.1993 DE 4315525**
23.11.1993 GB 9324045
09.03.1994 GB 9404544
14.03.1994 GB 9404928

(43) Date of publication of application:
06.03.1996 Bulletin 1996/10

(60) Divisional application:
96101147.5 / 0 729 751

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
94303128.6 / 0 624 366

(73) Proprietor: **Euro-Celtique S.A.**
Luxemburg (LU)

(72) Inventors:
- **Miller, Ronald Brown**
CH-4051 Basel (CH)
- **Leslie, Stewart Thomas**
Cambridge (GB)
- **Malkowska, Sandra Therese Antoinette**
Ely, Cambridgeshire (GB)
- **Smith, Kevin John**
Histon, Cambridge (GB)
- **Wimmer, Walter**
D-65549 Limburg (DE)
- **Winkler, Horst**
D-65550 Linter (DE)
- **Hahn, Udo**
D-56412 Nentershausen (DE)
- **Prater, Derek Allan**
Milton, Cambridge (GB)

(74) Representative: **Ruffles, Graham Keith**
MARKS & CLERK,
57-60 Lincoln's Inn Fields
London WC2A 3LS (GB)

(56) References cited:
EP-A- 0 147 780

- **CHEMICAL ABSTRACTS, vol. 112, no. 10, 5 March 1990, Columbus, Ohio, US; abstract no. 84206, & JP-A-01 149 717 (SHOWA DENKO K.K.) 12 June 1989**

Remarks:

•Divisional application 96101147.5 filed on 26/01/96.

•The file contains technical information submitted after the application was filed and not included in this specification

EP 0 699 436 B1

Printed by Jouve, 75001 PARIS (FR)

Description

[0001] The present invention relates to a controlled release preparation for oral administration, to processes for its preparation and to its medical use. In particular, the invention relates to a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof.

[0002] Tramadol, which has the chemical name (±)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol, or more particularly its hydrochloride salt, have been commercially available for many years for use in the treatment of moderate to severe pain; such preparations, however, do not provide a controlled release of the tramadol. Moreover, despite tramadol's long-standing use, controlled release preparations for oral administration containing tramadol as active ingredient have not even previously been described in the literature.

[0003] EP 147,780 relates to a drug delivery and mentions tramadol.

[0004] It is an object of the present invention to provide an oral controlled release tramadol preparation suitable for at least twelve-hourly (e.g. up to twenty-four hourly) administration for the treatment of pain.

[0005] The present invention therefore provides a controlled release preparation comprising tramadol or a pharmaceutically acceptable salt thereof for oral administration.

[0006] Suitable pharmaceutically acceptable salts of tramadol for use according to the present invention are those conventionally known in the art such as pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

[0007] A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Such a preparation maintains a drug concentration in the blood within the therapeutic range for 12 hours or more.

[0008] Thus, in accordance with the invention, there is provided an oral controlled release preparation of tramadol or a pharmaceutically acceptable salt thereof, effective for the treatment of moderate to severe pain for 12 hours or more, wherein:

(A) the oral controlled release preparation comprises the tramadol or a salt thereof incorporated in a controlled release matrix which includes one or more materials selected from (a) digestible C_8-C_{50} substituted or unsubstituted hydrocarbons such as; fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral or vegetable oils or waxes and (b) polyalkylene glycols; or

(B) the oral controlled release preparation comprises the tramadol or salt thereof in a controlled release matrix and in the form of multiparticulates, the matrix including a hydrophobic fusible carrier or diluent having a melting point of 35 to 140°C or a tablet obtained by compressing said multiparticulates; or

(C) the oral controlled release preparation comprises the tramadol or a salt thereof incorporated in a normal release matrix which is a spheroid comprising the tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent, the spheroid having a controlled release coating chosen from water insoluble waxes, water insoluble polymethacrylates and water insoluble celluloses.

[0009] The present inventors have found that in order to allow for controlled release tramadol over at least a twelve hour period following oral administration, the in vitro release rate preferably corresponds to the following % rate of tramadol released:

TABLE 1

TIME (H)	% RELEASED
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

[0010] Another preferred preparation especially suited for twice-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released:

TABLE 2

TIME (H)	% RELEASED
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

[0011] Yet another preferred preparation particularly suited for once-a-day dosing has an in-vitro release rate corresponding to the following % rate of tramadol released:

TABLE 3

TIME (H)	% RELEASED
1	0-50
2	0-75
4	10-95
8	35-100
12	55-100
16	70-100
24	>90

[0012] A still further preferred preparation in accordance with the invention also particularly suited for once-a-day dosing has an in vitro release rate corresponding to the following % rate of tramadol released.

TABLE 4

TIME (H)	% RELEASED
1	0-30
2	0-40
4	3-55
8	10-65
12	20-75
16	30-88
24	50-100
36	>80

[0013] More preferably a preparation for once-a-day dosing has an in vitro release rate substantially as follows;

TABLE 5

TIME (H)	% TRAMADOL RELEASED
1	10-30
2	17-37
4	27-47

TABLE 5 (continued)

TIME (H)	% TRAMADOL RELEASED
8	40-60
12	49-69
16	57-77

[0014] Another preferred dissolution rate in vitro upon release of the controlled release preparation for administration twice daily according to the invention, is between 5 and 50% (by weight) tramadol released after 1 hour, between 10 and 75% (by weight) tramadol released after 2 hours, between 20 and 95% (by weight) tramadol released after 4 hours, between 40 and 100% (by weight) tramadol released after 8 hours, more than 50% (by weight) tramadol released after 12 hours, more than 70% (by weight) released after 18 hours and more than 80% (by weight) tramadol released after 24 hours.

[0015] Furthermore, it is preferred in the case of a controlled release preparation for administration twice daily that after 8 hours following oral administration between 70 and 95% (by weight) tramadol is absorbed in vivo, between 77 and 97% (by weight) tramadol is absorbed after 10 hours and between 80 and 100% (by weight) tramadol is absorbed after 12 hours.

[0016] A formulation in accordance with the invention suitable for twice-a-day dosing may have a tmax of 1.5 to 8 hours, preferably 2 to 7 hours, and a W_{50} value in the range 7 to 16 hours.

[0017] A formulation in accordance with the invention suitable for once-a-day dosing may have a tmax in the range of 3 to 6 hours, preferably 4 to 5 hours and a W_{50} value in the range of 10 to 33 hours.

[0018] The W_{50} parameter defines the width of the plasma profile at 50% Cmax, i.e. the duration over which the plasma concentrations are equal to or greater than 50% of the peak concentration. The parameter is determined by linear interpolation of the observed data and represents the difference in time between the first (or only) upslope crossing and the last (or only) downslope crossing in the plasma profile.

[0019] The in vitro release rates mentioned herein are, except where otherwise specified, those obtained by measurement using the Ph. Eur. Paddle Method at 100rpm in 900ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270nm.

[0020] The controlled release preparation according to the invention preferably contains an analgesically effective amount of tramadol or a pharmaceutically acceptable salt thereof, conveniently in the range of from 50 to 400 mg, especially 100, 200, 300 or 400 mg (calculated as tramadol hydrochloride) per dosage unit.

[0021] The controlled release preparation according to the invention may be presented, for example, as granules, spheroids, pellets, multiparticulates, capsules, tablets, sachets, controlled release suspensions, or in any other suitable dosage form incorporating such granules, spheroids, pellets or multiparticulates.

[0022] The active ingredient in the preparation according to the invention may suitably be incorporated in a matrix. This may be any matrix that affords controlled release tramadol over at least a twelve hour period and preferably that affords in-vitro dissolution rates and in vivo absorption rates of tramadol within the ranges specified above. Preferably the matrix is a controlled release matrix. Alternatively, normal release matrices having a coating which provides for controlled release of the active ingredient may be used.

[0023] Suitable materials for inclusion in a controlled release matrix include

a) Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25 and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The preparation may conveniently contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(b) Polyalkylene glycols. The preparation may suitably contain up to 60% (by weight) of one or more polyalkylene glycols.

[0024] One particularly suitable controlled release matrix comprises one or more alkylcelluloses and one or more C_{12}-C_{36} aliphatic alcohols. The alkylcellulose is preferably C_1-C_6 alkyl cellulose, especially ethyl cellulose. The controlled release preparation according to the invention preferably contains from 1 to 20% (by weight), especially from 2 to 15% (by weight) of one or more alkylcelluloses.

[0025] The aliphatic alcohol may conveniently be lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or more preferably cetostearyl alcohol. The controlled release preparation suitably contains from 5 to 30% (by weight) of aliphatic alcohol, especially from 10 to 25% (by weight) of aliphatic alcohol.

[0026] Optionally the controlled release matrix may also contain other pharmaceutically acceptable ingredients which are conventional in the pharmaceutical art such as diluents, lubricants, binders, granulating aids, colourants, flavourants, surfactants, pH adjusters, anti-adherents and glidants, e.g. dibutyl sebacate, ammonium hydroxide, oleic acid and colloidal silica.

[0027] The controlled release preparation according to the invention may conveniently be film coated using any film coating material conventional in the pharmaceutical art. Preferably an aqueous film coating is used.

[0028] Alternatively, the controlled release preparation according to the invention may comprise a normal release matrix having a controlled release coating. Preferably the preparation comprises film coated spheroids containing the active ingredient and a spheronising agent.

[0029] The spheronising agent may be any suitable pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroids. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose used may suitably be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation).

[0030] Optionally the spheroids may contain other pharmaceutically acceptable ingredients conventional in the pharmaceutical art such as binders, bulking agents and colourants. Suitable binders include water soluble polymers, water soluble hydroxyalkyl celluloses such as hydroxypropylcellulose or water insoluble polymers (which may also contribute controlled release properties) such as acrylic polymers or copolymers for example ethylcellulose. Suitable bulking agents include lactose.

[0031] The spheroids are coated with a material which permits release of the active ingredient at a controlled rate in an aqueous medium. Suitable controlled release coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or water insoluble celluloses, particularly ethylcellulose. Optionally, water soluble polymers such as polyvinylpyrrolidone or water soluble celluloses such as hydroxypropylmethylcellulose or hydroxypropylcellulose may be included. Optionally other water soluble agents such as polysorbate 80 may be added.

[0032] Alternatively the drug may be coated onto inert non-pareil beads and the drug loaded beads coated with a material which permits control of the release of the active ingredient into the aqueous medium.

[0033] The controlled release preparation can be prepared by a process comprising incorporating tramadol or a pharmaceutically acceptable salt thereof in a controlled release matrix, for example by

(a) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof and one or more alkylcelluloses.
(b) mixing the alkylcellulose containing granules with one or more C_{12-36} aliphatic alcohols; and optionally
(c) shaping and compressing the granules, and film coating, if desired; or
(d) granulating a mixture comprising tramadol or a pharmaceutically acceptable salt thereof, lactose and one or more alkylcelluloses with one or more C_{12-36} aliphatic alcohol; and, optionally,
(e) shaping and compressing the granules, and film coating, if desired.

[0034] The controlled release preparation according to the invention may also be prepared in the form of film coated spheroids by

(a) granulating the mixture comprising tramadol or a pharmaceutically acceptable salt therefor and a spheronising agent;
(b) extruding the granulated mixture to give an extrudate;
(c) spheronising the extrudate until spheroids are formed; and
(d) coating the spheroids with a film coat.

[0035] One preferred form of unit dose form in accordance with the invention comprises a capsule filled with controlled release particles in the form of matrix multiparticulates essentially comprising the active ingredient, a hydrophobic fusible carrier or diluent and optionally a hydrophillic release modifier. In particular, the controlled release particles are preferably prepared by a process which comprises forming a mixture of dry active ingredient and fusible release control materials followed by mechanically working the mixture in a high speed mixer with an energy input sufficient to melt or soften the fusible material whereby it forms particles with the active ingredient. The resultant particles, after cooling, are suitably sieved to give particles having a size range from 0.1 to 3.0mm, preferably 0.25 to 2.0mm. An example according to the invention is described below which is suitable for the commercial production of dosage units.

[0036] When using such a processing technique it has been found that, in order most readily to achieve the desired release characteristics (both in vivo and in vitro as discussed above) the composition to be processed should comprises two essential ingredients namely:

(a) tramadol or salt thereof; and

(b) hydrophobic fusible carrier or diluent; optionally together with

(c) a release control component comprising a water-soluble fusible material or a particulate soluble or insoluble organic or inorganic material.

[0037] We have found that the total amount of tramadol or pharmaceutically acceptable salt thereof in the composition may vary within wide limits, for example from 10 to 90% by weight thereof.

[0038] The hydrophobic fusible component (b) should be a hydrophobic material such as a natural or synthetic wax or oil, for example hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, Beeswax, Carnauba wax or glyceryl monostearate, and suitably has a melting point of from 35 to 140°C, preferably 45 to 110°C.

[0039] The release modifying component (c), when a water soluble fusible material, is conveniently a polyethylene glycol and, when a particulate material, is conveniently a pharmaceutically acceptable material such as dicalcium phosphate or lactose.

[0040] Another preferred process for the manufacture of a formulation in accordance with the invention comprises

(a) mechanically working in a high-speed mixer, a mixture of tramadol or a pharmaceutically acceptable salt in particulate form and a particulate, hydrophobic fusible carrier or diluent having a melting point from 35 to 140°C and optionally a release control component comprising a water soluble fusible material, or a particulate soluble or insoluble organic or inorganic material at a speed and energy input which allows the carrier or diluent to melt or soften, whereby it forms agglomerates,

(b) breaking down the larger agglomerates to give controlled release seeds; and

(c) continuing mechanically working with optionally a further addition of low percentage of the carrier or diluent.

(d) optionally repeating steps (c) and possibly (b) one or more times.

[0041] This process is capable of giving a high yield (over 80%) of particles in a desired size range, with a desired uniformity of release rate of tramadol or salt thereof.

[0042] The resulting particles may be sieved to eliminate any over-or undersized material then formed into the desired dosage units by for example, encapsulation into hard gelatin capsules containing the required dose of the active substance or by compression into tablets.

[0043] In this method in accordance with the invention preferaby all the tramadol or salt thereof is added in step (a) together with a major portion of the hydrophobic fusible release control material used. Preferably the amount of fusible release control material added in step (a) is between 10% and 90% w/w of the total amount of ingredients added in the entire manufacturing operation, more preferably between 20% and 70% w/w.

[0044] Stage (a) of the process may be carried out in conventional high speed mixers with a standard stainless steel interior, e.g. a Collette Vactron 75 or equivalent mixer. The mixture is processed until a bed temperature about 40°C or above is achieved and the resulting mixture acquires a cohesive granular texture, with particle sizes ranging from about 1-3mm to fine powder in the case of non-aggregated original material. Such material, in the case of the embodiments described below, has the appearance of agglomerates which upon cooling below 40°C have structural integrity and resistance to crushing between the fingers. At this stage the agglomerates are of an irregular size, shape and appearance.

[0045] The agglomerates are preferably allowed to cool. The temperature to which it cools is not critical and a temperature in the range room temperature to 37°C may be conveniently used.

[0046] The agglomerates are broken down by any suitable means, which will comminute oversize agglomerates and produce a mixture of powder and small particles preferably with a diameter under 2mm. It is currently preferred to carry out the classification using a Jackson Crockatt granulator using a suitable sized mesh, or a Comil with an appropriate sized screen. We have found that if too small a mesh size is used in the aforementioned apparatus the agglomerates melting under the action of the beater or impeller will clog the mesh and prevent further throughput of mixture, thus reducing yield. A mesh size of 12 has been found adequate.

[0047] The classified material is returned to the high speed mixer and processing continued. It is believed that this leads to cementation of the finer particles into particles of uniform size range.

[0048] In one preferred form of the method of the invention processing of the classified materials is continued, until the hydrophobic fusible materials used begin to soften/melt and optionally additional hydrophobic fusible material is then added. Mixing is continued until the mixture has been transformed into particles of the desired predetermined size

range.

[0049] In order to ensure uniform energy input into the ingredients in the high speed mixer it is preferred to supply at least part of the energy by means of microwave energy.

[0050] Energy may also be delivered through other means such as by a heating jacket or via the mixer impeller and chopper blades.

[0051] After the particles have been formed they are cooled or allowed to cool, and may then be sieved to remove any over or undersized material.

[0052] The resulting particles may be used to prepare dosage units in accordance with the invention in the form of e.g. tablets or capsules in manners known per se.

[0053] We have also found that particles containing tramadol or a salt thereof produced by a melt processing as described in application PCT/SE93/00225 and the process described and claimed in our prior unpublished UK application No. 9324045.5 filed on 23 November 1993 as well as the process described herein are particularly useful for processing into the form of tablets.

[0054] We have found that by suitable selection of the materials used in forming the particles and in the tabletting and the proportions in which they are used, enables a significant degree of control in the ultimate dissolution and release rates of the tramadol or salt thereof from the compressed tablets.

[0055] Usually, to form a tablet in accordance with the invention, particles prepared as described above will be admixed with tabletting excipients e.g. one or more of the standard excipients' such as diluents, lubricants, binding agents, flow aids, disintegrating agents, surface active agents or water soluble polymeric materials.

[0056] Suitable diluents are e.g. microcrystalline cellulose, lactose and dicalcium phosphate. Suitable lubricants are e.g. magnesium stearate and sodium stearyl fumarate.

Suitable binding agents are e.g. hydroxypropyl methyl cellulose, polyvidone and methyl cellulose.

[0057] Suitable disintegrating agents are starch, sodium starch glycolate, crospovidone and croscarmalose sodium. Suitable surface active are Poloxamer 188®, polysorbate 80 and sodium lauryl sulfate. Suitable flow aids are talc colloidal anhydrous silica.

Suitable water soluble polymers are PEG with molecular weights in the range 1000 to 6000.

[0058] To produce tablets in accordance with the invention, particles produced in accordance with the invention may be mixed or blended with the desired excipient(s), if any, using conventional procedures, e.g. using a Y-Cone or bin-blender and the resulting mixture compressed according to conventional tabletting procedure using a suitable size tabletting mould. Tablets can be produced using conventional tabletting machines, and in the embodiments described below were produced on standard single punch F3 Manesty machine or Kilian RLE15 rotary tablet machine.

[0059] Generally speaking we find that even with such a highly water soluble active agent as tramadol or salt thereof tablets formed by compression according to standard methods give very low release rates of the active ingredient e.g. corresponding to release over a period of greater than 24 hours, say more than 36. We have found that the release profile can be adjusted in a number of ways. For instance a higher loading of the drug will be associated with increased release rates; the use of larger proportions of the water soluble fusible material in the particles or surface active agent in the tabletting formulation will also be associated with a higher release rate of the active ingredient. By controlling the relative amounts of these ingredients it is possible to adjust the release profile of the tramadol or salt thereof.

[0060] In order that the invention may be well understood the following examples are given by way of illustration only. Examples 1 to 3 are Reference Examples and relate to preparation is accordance with present application 94303128.6.

Example 1

[0061] Tablets having the following formulation were prepared:

	mg/tablet
Tramadol Hydrochloride	100
Lactose Ph. Eur.	68.0
Ethylcellulose (Surelease® 25% solids)	15
Purified Water Ph. Eur.	13.3*
Cetostearyl Alcohol Ph. Eur. (Dehydag wax 0)	42.00
Magnesium Stearate Ph. Eur.	2.00
Purified Talc Ph. Eur.	3.00
	230.00

* Removed during processing.

[0062] Tramadol hydrochloride (100mg) and lactose (68mg) were granulated, transferred to a fluid bed granulator and sprayed with ethylcellulose (15mg) and water. The granules were then dried at 60°C and passed through a lmm screen.

[0063] To the warmed tramadol containing granules was added molten cetostearyl alcohol (42mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets.

[0064] The tablets were coated with a film coat having the formulation given below.

	mg/tablet
Hydropropylmethylcellulose Ph. Eur. 15 cps (Methocel E15)	0.770
Hydroxypropylmethylcellulose (Ph. Eur. 5 cps (Methocel E5)	3.87
Opaspray M-1-7111B (33% solids)	2.57
Polyethylene glycol 400 USNF	0.520
Purified Talc Ph. Eur.	0.270
Purified Water Ph. Eur.	55.52 *

* Remove during processing.

Example 2

[0065] Tablets having the following formulation were prepared:

	mg/tablet
Tramadol hydrochloride	100.0
Lactose Ph. Eur.	58.0
Ethylcellulose USNF (Ethocel 45 CP)	15.0
Cetostearyl alcohol Ph. Eur. (Dehydag wax O)	52.0
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

[0066] A mixture of tramadol hydrochloride (100mg), lactose (58mg) and ethylcellulose (15mg) was granulated whilst adding molten cetostearyl alcohol (52mg) and the whole was mixed thoroughly. The granules were allowed to cool and sieved through a 1.6mm screen. Purified talc and magnesium stearate were added and mixed with the granules. The granules were then compressed into tablets which were coated with a film coat having the formulation given in Example 1.

Example 3

[0067] Film coated tablets were produced following the procedure described in Example 2 and having the following formulation:

	mg/tablet
Tramadol hydrochloride	100.00
Lactose Ph. Eur.	70.50
Hydroxyethylcellulose Ph. Eur.	12.50
Cetostearyl alcohol Ph. Eur.	42.00
Magnesium stearate Ph. Eur.	2.00
Purified talc Ph. Eur.	3.00

In vitro dissolution studies

[0068] In vitro dissolution studies were conducted on tablets prepared as described above. Results are given in Table 1.

TABLE 1

WT % TRAMADOL RELEASED			
Time (h)	Example 1	Example 2*	Example 3
1	39	35	43
2	52	47	60
4	67	62	84
8	82	78	97
12	90	86	-

* Measured on tablet core

[0069] In a trial involving 12 healthy volunteers the serum levels of tramadol following administration of one tablet according to Example 2 was found to be as illustrated in Figure 1.

Example 4 and 5

[0070] Particles having the formulations given in Table II below , were prepared by the steps of:

i. Placing the ingredients (a) and (c) (total batch weight 0.7kg) in the bowl of a 10 litre capacity Collette Gral Mixer (or equivalent) equipped with variable speed mixing and granulating blades;

ii. Mixing the ingredients at about 150-1000rpm whilst applying heat until the contents of the bowl are agglomerated.

iii. Classifying the agglomerated material by passage through a Comil and/or Jackson Crockatt to obtain controlled release seeds.

iv. Warming and mixing the classified material in the bowl of a 10 litre Collette Gral, until uniform multiparticulates of the desired pre-determined size range are formed in yield of greater than 80%. This takes approximately 5 minutes.

v. Discharging the multiparticulates from the mixer and sieving them to separate out the multiparticulates collected between 0.5 and 2mm aperture sieves.

TABLE II

Example	4	5
(a) Tramadol HCl (Wt%)	50	75
(b) Hydrogenated Vegetable Oil (Wt%)	50	25

Example 6

[0071] Samples of the particles from Example 4 were blended with magnesium stearate and purified talc using a Y-Cone or bin-blender. The blended mixture was then compressed using either (1) 14 x 6mm, (2) 16 x 7mm or (3) 18.6 x 7.5mm capsule shaped tooling on a single punch F3 Manesty tabletting machine to give tablets giving 200, 300 and 400mg of tramadol HCl. The ingredients per dosage unit amounted to the following:

TABLE III			
TABLET INGREDIENT	MG/TABLET		
	1	2	3
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	200	300	400
Sub Total	400	600	800
Purified Talc	12.63	18.95	25.26
Magnesium Stearate	8.42	12.63	16.84

[0072] The tablets were assessed by the dissolution using Ph. Eur. Paddle Method 100 rpm, 0.1 N HCl.

[0073] To assess the non-compressed particles the Ph Eur. Paddle was replaced by a modified Ph Eur. Basket.

[0074] The results are shown in Table IV below;

TABLE IV

HOURS AFTER START OF TEST	Particles	Tablet 1	Tablet 2	Tablet 3
	% TRAMADOL HCl RELEASED			
1	54	16	15	15
2	68	23	20	21
3	76	28	25	25
4	82	32	28	28
6	89	40	35	35
8	93	46	41	40
10	96	50	45	45
12	98	55	49	49
16	100	63	57	56
20	NR	70	63	NR

[0075] These results confirm the effectiveness of the tabletting in reducing the release rate.

Example 7

[0076] Samples of the particles from Example 5 were then tabletted using a procedure similar to Example 3 and the ingredients per unit dosage amounted to:

TABLE V			
TABLET INGREDIENT	MG/TABLET		
	4	5	6
Tramadol Hcl	200	300	400
Hydrogenated Vegetable Oil	66.7	100	133
Sub Total	266.7	400	533
Purified Talc	7.63	11.44	15.25
Magnesium Stearate	5.16	7.63	10.17

[0077] The tablets and samples of non-compressed multiparticulates (each sample containing 400mg of tramadol hydrochloride) were assessed by the dissolution method also described above. The results are shown in Table VI below;

TABLE VI

HOURS AFTER START OF TEST	Particles	Tablet 4	Tablet 5	Tablet 6
	% TRAMADOL HCl RELEASED			
1	77	43	40	42
2	92	64	55	56
3	98	75	65	66
4	100	83	72	73
6	102	94	83	84
8	102	100	91	91
10	102	NR	96	97

[0078] These results show that by increasing the loading of the highly water soluble tramadol hydrochloride (75% w/w in this example compared with 50% w/w in Example 6) a significantly faster release rate of the active ingredient can be achieved.

Example 8

[0079] Example 4 was repeated but with the following formulation:

Tramadol HCl	200 mg/tablet
Hydrogenated Vegetable Oil	163.0 mg/tablet

[0080] The resulting multiparticulates were blended as described in Example 6 with the following;

Purified Talc	11.5 mg/tablet
Magnesium Stearate	7.66 mg/tablet

[0081] The blend was then compressed as described in Example 6 but using 15mm x 6.5mm normal concave capsule shaped plain/plain punches.

[0082] The resulting tablets were then assessed by the dissolution method described above. The results are shown in Table V.

HOURS AFTER START OF TEST	% TRAMADOL HCl RELEASED
1	20
2	27
3	32
4	37
6	44
8	50
10	55
12	60
16	67
20	73
24	77

[0083] In a trial involving five healthy male volunteers the plasma profile resulting from single dose administrations of the above tablet are shown in Figure 2 in comparison to the administration of a commercial preparation of Tramadol drops 100mg.

Claims

1. An oral controlled release preparation of tramadol or a pharmaceutically acceptable salt thereof, effective for the treatment of moderate to severe pain for 12 hours or more, wherein:

   (A) the oral controlled release preparation comprises the tramadol or a salt thereof incorporated in a controlled release matrix which includes one or more materials selected from (a) digestible C_8-C_{50} substituted or unsubstituted hydrocarbons such as; fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral or vegetable oils or waxes and (b) polyalkylene glycols; or
   (B) the oral controlled release preparation comprises the tramadol or salt thereof in a controlled release matrix and in the form of multiparticulates, the matrix including a hydrophobic fusible carrier or diluent having a melting point of 35 to 140°C or a tablet obtained by compressing said multiparticulates; or
   (C) the oral controlled release preparation comprises the tramadol or a salt thereof incorporated in a normal release matrix which is a spheroid comprising the tramadol or a pharmaceutically acceptable salt thereof and a spheronising agent, the spheroid having a controlled release coating chosen from water insoluble waxes, water insoluble polymethacrylates and water insoluble celluloses.

2. A preparation according to Claim 1, wherein the hydrochloride salt of tramadol is employed as the pharmaceutically acceptable salt.

3. A preparation according to claim 1 or 2, wherein the amount of tramadol or a pharmaceutically acceptable salt is in the range of from 50 to 400 mg (calculated as tramadol hydrochloride).

4. A preparation according to claim 1, 2 or 3, wherein in (A) the preparation contains up to 60% by weight of the component (a).

5. A preparation according to claim 4, wherein the component (a) includes a fatty alcohol present in an amount of 5 to 30% by weight of the preparation.

6. A preparation according to claim 5, wherein the fatty alcohol is chosen from lauryl alcohol, myristyl alcohol, stearyl alcohol, cetyl alcohol and cetostearyl alcohol.

7. A preparation according to claim 6, wherein the fatty alcohol is cetyl alcohol.

8. A preparation according to any preceding claim, wherein in (A) the matrix includes one or more alkyl celluloses and one or more C_{12} to C_{36} aliphatic alcohols.

9. A preparation according to claim 1, wherein in (B) the hydrophobic fusible carrier or diluent is a natural or synthetic wax or oil.

10. A preparation according to claim 9, wherein the hydrophobic fusible carrier or diluent is hydrogenated vegetable oil, hydrogenated castor oil, microcrystalline wax, beeswax, carnauba wax or glyceryl monostearate.

11. A preparation according to any of claims 9 or 10, wherein the matrix further includes a release control component comprising a water fusible soluble material or a particulate soluble or insoluble organic or inorganic material.

12. A preparation according to claim 1, 2 or 3 wherein in (C) the spheroids contain other pharmaceutically acceptable ingredients such as a binder, a bulking agent and/or a colourant.

13. A preparation according to claim 12, wherein the binder is a water-soluble polymer, a water-soluble hydroxyalkylcellulose or a water-insoluble polymer.

14. A preparation according to claim 13, wherein the binder which is a water insoluble polymer also contributes controlled release properties.

15. A preparation according to claim 13, wherein the water soluble hydroxyalkylcellulose is hydroxypropylcellulose.

16. A preparation according to any of claims 12 to 15, wherein said bulking agent is lactose.

17. An oral controlled release preparation according to any preceding claim, wherein the in vitro release rate of tramadol when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm, is:

time (h)	% released
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80.

18. An oral controlled release preparation according to any preceding claim, wherein the in vitro release rate of tramadol when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm, is:

time (h)	% released
1	5-50
2	10-75
4	20-95

(continued)

time (h)	% released
8	40-100
12	>50
18	>70
24	>80

19. An oral controlled release preparation according to any preceding claim, wherein the in vitro release rate of tramadol when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm. is:

time (h)	% released
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

20. An oral controlled release preparation according to any preceding claim, wherein the in vitro release rate of tramadol when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1 N hydrochloric acid at 37°C and using UV detection at 270 nm is:

time (h)	% released
1	10-30
2	17-37
4	27-47
8	40-60
12	49-69
16	57-77

Patentansprüche

1. Orales Arzneimittel mit kontrollierter Wirkstoffabgabe, das Tramadol oder ein pharmazeutisch annehmbares Salz davon enthält und für die Behandlung mäßiger bis starker Schmerzen über 12 Stunden oder länger wirksam ist, wobei

   (A) das orale Arzneimittel mit kontrollierter Wirkstoffabgabe das Tramadol oder ein Salz davon in einer Matrix mit kontrollierter Freisetzung enthält, die einen oder mehrere Stoffe aufweist, ausgewählt unter (a) verdaulichen substituierten oder nichtsubstituierten C_8-C_{50}-Kohlewasserstoffen, wie z. B. Fettsäuren, Fettalkoholen, Glycerylestern von Fettsäuren, Mineral- oder Pflanzenölen oder -wachsen und (b) Polyalkylenalkoholen; oder

   (B) das orale Arzneimittel mit kontrollierter Wirkstoffabgabe das Tramadol oder ein Salz davon in einer Matrix mit kontrollierter Freisetzung in Form von mehrteiligen Feststoffteilchen aufweist, wobei die Matrix einen hydrophoben schmelzbaren Träger oder ein Verdünnungsmittel mit einem Schmelzpunkt von 35 bis 140°C oder eine durch Pressen der mehrteiligen Feststoffteilchen gewonnene Tablette aufweist; oder

   (C) das orale Arzneimittel mit kontrollierter Wirkstoffabgabe das Tramadol oder ein Salz davon in einer Matrix mit normaler Freisetzung aufweist, die ein Sphäroid ist, das Tramadol oder ein pharmazeutisch annehmbares

Salz davon und ein sphäroidisierendes Mittel aufweist, wobei das Sphäroid eine Beschichtung mit kontrollierter Freisetzung aufweist, die unter wasserunlöslichen Wachsen, wasserunlöslichen Polymethacrylaten und wasserunlöslichen Cellulosen ausgewählt ist.

2. Arzneimittel nach Anspruch 1, wobei das Hydrochloridsalz von Tramadol als pharmazeutisch annehmbares Salz verwendet wird.

3. Arzneimittel nach Anspruch 1 oder 2, wobei die Menge von Tramadol oder eines pharmazeutisch annehmbaren Salzes davon im Bereich von 50 bis 400 mg (berechnet als Tramadolhydrochlorid) liegt.

4. Arzneimittel nach Anspruch 1, 2 oder 3, wobei das Arzneimittel in (A) bis zu 60 Gew.-% der Komponente (a) enthält.

5. Arzneimittel nach Anspruch 4, wobei die Komponente (a) einen Fettalkohol in einem Anteil von 5 bis 30 Gew.-% des Arzneimittels enthält.

6. Arzneimittel nach Anspruch 5, wobei der Fettalkohol unter Laurylalkohol, Myristylalkohol, Stearylalkohol, Cetylalkohol und Cetostearylalkohol ausgewählt ist.

7. Arzneimittel nach Anspruch 6, wobei der Fettalkohol Cetylalkohol ist.

8. Arzneimittel nach einem der vorstehenden Ansprüche, wobei in (A) die Matrix eine oder mehrere Alkylcellulosen und einen oder mehrere aliphatische C_{12}- bis C_{36}-Alkohole enthält.

9. Arzneimittel nach Anspruch 1, wobei in (B) der hydrophobe schmelzbare Träger oder das Verdünnungsmittel ein natürliches oder synthetisches Wachs oder Öl ist.

10. Arzneimittel nach Anspruch 9, wobei der hydrophobe schmelzbare Träger oder das Verdünnungsmittel hydriertes Pflanzenöl, hydriertes Castoröl, mikrokristallines Wachs, Bienenwachs, Carnaubawachs oder Glycerylmonostearat ist.

11. Arzneimittel nach einem der Ansprüche 9 oder 10, wobei die Matrix ferner eine Komponente mit kontrollierter Freisetzung enthält, die ein in Wasser schmelzbares lösliches Material oder ein teilchenförmiges lösliches oder unlösliches organisches oder anorganisches Material aufweist.

12. Arzneimittel nach Anspruch 1, 2 oder 3, wobei in (C) die Sphäroide weitere pharmazeutisch annehmbare Bestandteile enthalten, wie z. B. ein Bindemittel, ein Füllmaterial und/oder ein Färbemittel.

13. Arzneimittel nach Anspruch 12, wobei das Bindemittel ein wasserlösliches Polymer, eine wasserlösliche Hydroxyalkylcellulose oder ein wasserunlösliches Polymer ist.

14. Arzneimittel nach Anspruch 13, wobei das Bindemittel, das ein wasserunlösliches Polymer ist, gleichfalls kontrollierte Freisetzungseigenschaften beiträgt.

15. Arzneimittel nach Anspruch 13, wobei die wasserlösliche Hydroxyalkylcellulose Hydroxypropylcellulose ist.

16. Arzneimittel nach einem der Ansprüche 12 bis 15, wobei das Füllmaterial Lactose ist.

17. Orales Arzneimittel mit kontrollierter Wirkstoffabgabe nach einem der vorstehenden Ansprüche, wobei die In-vitro-Freisetzungsrate von Tramadol, gemessen unter Anwendung der Paddelmethode gemäß Eur. Pharmakopoe bei 100 U/min in 900 ml 0,1N Salzsäure bei 37°C und mit UV-Nachweis bei 270 nm, den folgenden Verlauf aufweist:

Zeit (h)	Freisetzung in %
1	0-50
2	0-75
4	3-95

(fortgesetzt)

Zeit (h)	Freisetzung in %
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

18. Orales Arzneimittel mit kontrollierter Wirkstoffabgabe nach einem der vorstehenden Ansprüche, wobei die In-vitro-Freisetzungsrate von Tramadol, gemessen unter Anwendung der Paddelmethode gemäß Eur. Pharmakopoe bei 100 U/min in 900 ml 0,1N Salzsäure bei 37°C und mit UV-Nachweis bei 270 nm, den folgenden Verlauf aufweist:

Zeit (h)	Freisetzung in %
1	5-50
2	10-75
4	20-95
8	40-100
12	>50
18	>70
24	>80

19. Orales Arzneimittel mit kontrollierter Wirkstoffabgabe nach einem der vorstehenden Ansprüche, wobei die In-vitro-Freisetzungsrate von Tramadol, gemessen unter Anwendung der Paddelmethode gemäß Eur. Pharmakopoe bei 100 U/min in 900 ml 0,1N Salzsäure bei 37°C und mit UV-Nachweis bei 270 nm, den folgenden Verlauf aufweist:

Zeit (h)	Freisetzung in %
1	20-50
2	40-75
4	60-95
8	80-100
12	90-100

20. Orales Arzneimittel mit kontrollierter Wirkstoffabgabe nach einem der vorstehenden Ansprüche, wobei die In-vitro-Freisetzungsrate von Tramadol, gemessen unter Anwendung der Paddelmethode gemäß Eur. Pharmakopoe bei 100 U/min in 900 ml 0,1N Salzsäure bei 37°C und mit UV-Nachweis bei 270 nm, den folgenden Verlauf aufweist:

Zeit (h)	Freisetzung in %
1	10-30
2	17-37
4	27-47
8	40-60
12	49-69
16	57-77

Revendications

1. Préparation orale à libération contrôlée de tramadol ou d'un sel pharmaceutiquement acceptable correspondant, efficace pour le traitement d'une douleur modérée à sévère pendant 12 heures ou plus, dans laquelle:

   (A) la préparation orale à libération contrôlée comprend le tramadol ou un sel correspondant, incorporé dans une matrice à libération contrôlée qui comporte une ou plusieurs matières choisies parmi (a) les hydrocarbures digestibles substitués ou non substitués en C_8-C_{50}, tels que; des acides gras, des alcools gras, des esters glycériques d'acides gras, des cires ou des huiles minérales ou végétales et (b) des polyalkylène-glycols; ou

   (B) la préparation orale à libération contrôlée comprend le tramadol ou un sel correspondant dans une matrice à libération contrôlée et sous la forme de matières multi-particulaires, la matrice comportant un véhicule ou diluant hydrophobe fusible ayant un point de fusion de 35 à 140°C ou un comprimé obtenu par compression des matières multi-particulaires; ou

   (C) la préparation orale à libération contrôlée comprend le tramadol ou un sel correspondant, incorporé dans une matrice à libération normale qui est un sphéroïde comportant le tramadol ou un sel pharmaceutiquement acceptable correspondant et un agent de sphéroïdation, le sphéroïde possédant un revêtement à libération contrôlée choisi parmi les cires insolubles dans l'eau, les polyméthacrylates insolubles dans l'eau et les celluloses insolubles dans l'eau.

2. Préparation suivant la revendication 1, dans laquelle le chlorhydrate de tramadol est employé en tant que sel pharmaceutiquement acceptable.

3. Préparation suivant la revendication 1 ou 2, dans laquelle la quantité de tramadol ou de sel pharmaceutiquement acceptable se situe dans le domaine allant de 50 à 400 mg (calculée comme chlorhydrate de tramadol).

4. Préparation suivant la revendication 1, 2 ou 3, dans laquelle dans (A) la préparation contient jusqu'à 60% en poids de la composante (a).

5. Préparation suivant la revendication 4, dans laquelle la composante (a) comporte un alcool gras présent en une quantité de 5 à 30% en poids de la préparation.

6. Préparation suivant la revendication 5, dans laquelle l'alcool gras est choisi parmi l'alcool laurique, l'alcool myristique, l'alcool stéarique, l'alcool cétylique et l'alcool cétostéarique.

7. Préparation suivant la revendication 6, dans laquelle l'alcool gras est l'alcool cétylique.

8. Préparation suivant l'une quelconque des revendications qui précèdent, dans laquelle en (A) la matrice comporte une ou plusieurs alkylcelluloses et un ou plusieurs alcools aliphatiques en C_{12} à C_{36}.

9. A préparation suivant la revendication 1, dans laquelle en (B) le véhicule ou diluant hydrophobe fusible est une huile ou une cire naturelle ou synthétique.

10. Préparation suivant la revendication 9, dans laquelle le véhicule ou diluant hydrophobe fusible est une huile végétale hydrogénée, une huile de ricin hydrogénée, une cire microcristalline; une cire d'abeille, une cire de Carnauba ou le monostéarate de glycérol.

11. Préparation suivant l'une quelconque des revendications 9 ou 10, dans laquelle la matrice comporte par ailleurs une composante de contrôle de la libération comprenant une matière fusible soluble dans l'eau ou une matière particulaire organique ou inorganique, soluble ou insoluble.

12. Préparation suivant la revendication 1, 2 ou 3 dans laquelle en (C) les sphéroïdes contiennent d'autres ingrédients pharmaceutiquement acceptables, tels qu'un liant, un agent de gonflement et/ou un colorant.

13. Préparation suivant la revendication 12, dans laquelle le liant est un polymère soluble dans l'eau, une hydroxyalkylcellulose soluble dans l'eau ou un polymère insoluble dans l'eau.

14. Préparation suivant la revendication 13, dans laquelle le liant, qui est un polymère insoluble dans l'eau, apporte également des propriétés de libération contrôlée.

15. Préparation suivant la revendication 13, dans laquelle l'hydroxyalkylcellulose soluble dans l'eau est l'hydroxypropylcellulose.

16. Préparation suivant l'une quelconque des revendications 12 à 15, dans laquelle ledit agent de gonflement est le lactose.

17. Préparation orale à libération contrôlée suivant l'une quelconque des revendications qui précèdent, dans laquelle la vitesse de libération in vitro de tramadol, lorsqu'elle est mesurée en appliquant la méthode Ph. Eur. Paddle à 100 tours/minute, dans 900 ml d'acide chlorhydrique 0,1 N à 37°C et en utilisant une détection aux UV à 270 nm, est comme suit:

TEMPS (h)	LIBERATION (%)
1	0-50
2	0-75
4	3-95
8	10-100
12	20-100
16	30-100
24	50-100
36	>80

18. Préparation orale à libération contrôlée suivant l'une quelconque des revendications qui précèdent, dans laquelle la vitesse de libération in vitro de tramadol, lorsqu'elle est mesurée en appliquant la méthode Ph. Eur. Paddle à 100 tours/minute, dans 900 ml d'acide chlorhydrique 0,1 N à 37°C et en utilisant une détection aux UV à 270 nm, est comme suit:

TEMPS (h)	LIBERATION (%)
1	5-50
2	10-75
4	20-95
8	40-100
12	> 50
18	> 70
24	> 80

19. Préparation orale à libération contrôlée suivant l'une quelconque des revendications qui précèdent, dans laquelle la vitesse de libération in vitro de tramadol, lorsqu'elle est mesurée en appliquant la méthode Ph. Eur. Paddle à 100 tours/minute, dans 900 ml d'acide chlorhydrique 0,1 N à 37°C et en utilisant une détection aux UV à 2 nm, est comme suit:

TEMPS (h)	LIBERATION (%)
1	20-50
2	40-75
4	60-95
8	80-100

(suite)

TEMPS (h)	LIBERATION (%)
12	90-100

20. Préparation orale à libération contrôlée suivant l'une quelconque des revendications qui précèdent, dans laquelle la vitesse de libération in vitro de tramadol, lorsqu'elle est mesurée en appliquant la méthode Ph. Eur. Paddle à 100 tours/minute, dans 900 ml d'acide chlorhydrique 0,1 N à 37°C et en utilisant une détection aux UV à 270 nm, est comme suit:

TEMPS (h)	LIBERATION (%)
1	10-30
2	17-37
4	27-47
8	40-60
2	49-69
16	57-77

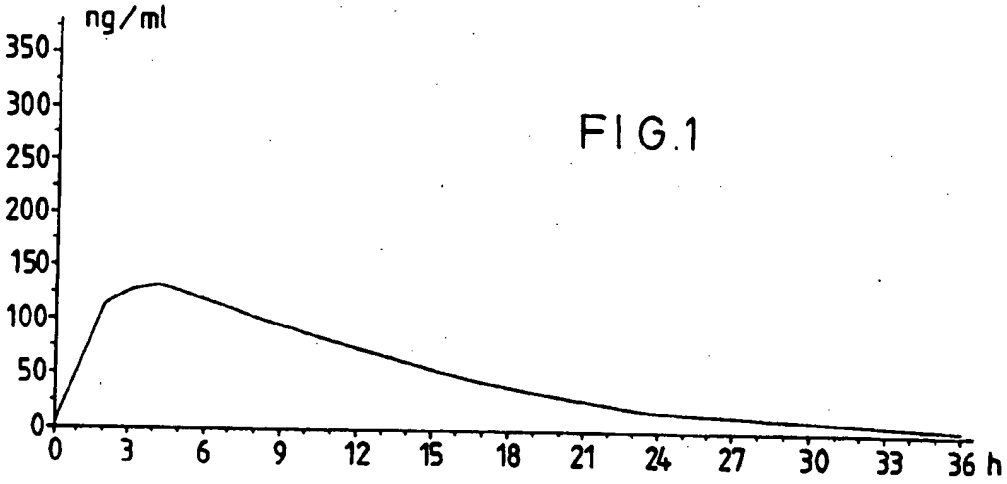
ng/ml
350
300
250
200
150
100
50
0
0
3
6
9
12
15
18
21
24
27
30
33
36 h

FIG.1

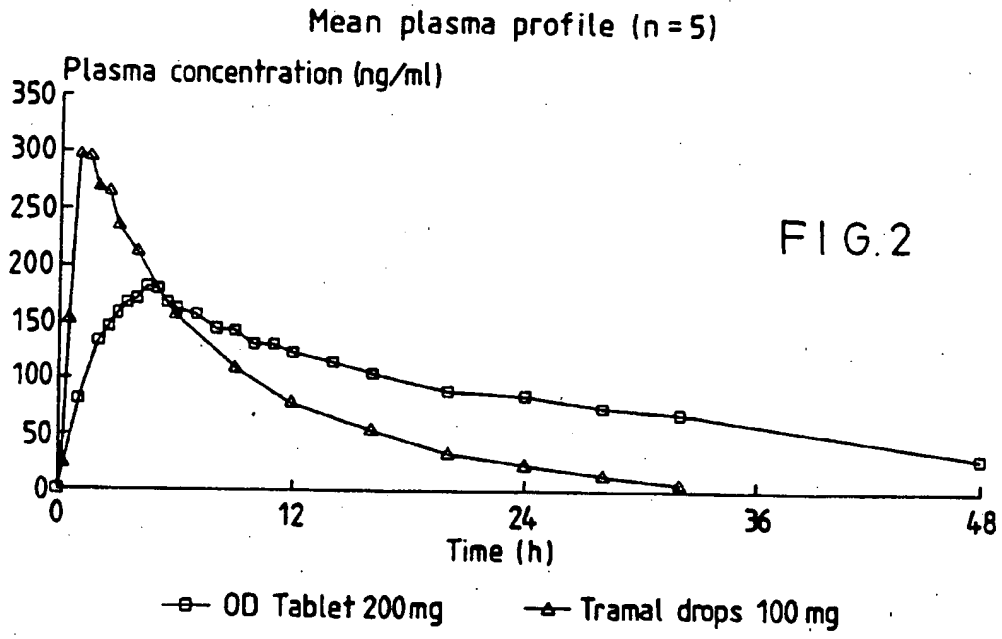
Mean plasma profile (n = 5)
Plasma concentration (ng/ml)
350
300
250
200
150
100
50
0
0
12
24
36
48
Time (h)
OD Tablet 200mg
Tramal drops 100 mg

FIG.2